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LEPROSY—THE PRESENCE OF ACID-FAST BACILLI IN THE CIRCULATING BLOOD AND EXCRETIONS

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In the literature and text books on leprosy, there is much divergence of opinion regarding the presence of the acid-fast bacillus of leprosy in the blood and excretions of patients. The present paper is the result of systematic search in an attempt to analyze the cases occurring at the Penikese Leper Colony and to determine whether the acid-fast bacillus can or cannot be found in the blood, urine, feces, sputum, nasal mucus, and other excretions and discharges, so as to eliminate possible errors in research along other lines now being carried out.

REVIEW

The acid-fast bacillus of leprosy was originally discovered and described by Hansen in 1873-74, and later by Neisser, in the tissues and scrapings from lesions of leprosy. Since then, much attention has been paid to the manner in which the disease is communicated from one person to another, and to the site of the original lesion. In the last few years, the part insects play in spreading the disease has received considerable notice.

Nasal lesions with reference to the presence of the leprosy bacillus.—Ziemssen states that among the parts most affected are the nasal and oral mucous membranes and that even in the early stages ulcerations covered with corresponding crusts are met with, especially in the nose. Tilbury Fox in nearly the same terms calls attention to the involvement of the nasal mucous membrane. Arning and also Danielssen (quoted by Uhlenhuth and Steffenhagen) and Boeck state that leprous ulcerations of the nose occur in anesthesic cases which otherwise present no ulcerations, and Arning in two cases found numerous bacilli in the discharge from nasal sores. Besnier states that the nasal mucus teems with bacilli. Leloir, however, notes that if the surfaces are infected, then the bacilli will be found in the nasal mucus. Goldschmidt advocates the examination of the nasal mucous membrane and nasal mucus. Falkao points out the fact of the prevalence of lesions in the nose and the frequent presence of the leprosy bacillus. Bibb occasionally found the bacillus in the secretions from the nose. Koch and Sticker state that the primary affection is in the nose, Koch basing his opinion on his experience of examining some 400 patients in India and Egypt. Kolle also directs attention to the condition of the nose and the nasopharyngeal passages in cases of leprosy. Gluck — altho not specifically examining nasal secretions — describes in great detail the pathologic changes and the presence of the bacillus there. Jeanselme and Laurence consider that the bacilliladen nasal mucus plays a rôle in the propagation of the disease. Fraenkel presents the case of a man who had suffered for three years from epistaxis and in whom he had found the bacillus in the nasal mucus. Thiroux found the bacillus in 39 percent of his cases. Black states that almost all mixed and nodular cases suffer from rhinitis and discharge bacilli with the nasal secretion. Thomson reports one case in which he found the typical bacillus of leprosy in the smear of the nasal mucus. Brinckerhoff and Moore lay importance on the examination of the nasal secretions for the detection of incipient cases of leprosy. Their positive results demonstrate the value of this means of bacteriologic diagnosis. Kitasato reports the presence of bacilli in 50 to 60 percent of the secretions of patients. Marchoux, after treating the patient with potassium iodid to produce a rhinitis, discovered in the nasal mucus the bacillus of leprosy. Leboeuf found the bacillus in the nasal mucus in 159 of 224 cases, the greatest percentage being among the tubercular patients. Jeanselme states that the nasal symptoms are commonly the first indication of the disease and thinks the rhinitis of leprosy one of the most prominent agents in the dissemination of the disease. Joyeux also reports the finding of bacilli in nasal mucus during attacks of coryza. Manson states that the bacillus is abundant in the purulent discharges from the nose. He indicates here that ulceration of the nasal tissues must have occurred. Hollmann presents an excellent article on the results of 329 examinations of the secretions of lepers, demonstrating the presence of the leprosy bacillus in 89.6 percent of nodular cases, 45.4 percent of anesthesic, and 66.6 percent of mixed cases. Thibault, in thirty cases examined, found the bacillus in the nasal mucus of twenty, potassium iodid having been used to provoke secretions. Leredde and Pautrier, and Pautrier report positive results in four cases after having given potassium iodid to induce rhinitis. Hollmann, as the result of the examination of the nasal mucous membrane of 500 lepers, found that there were lesions present in 410 cases.

While not all investigators are of the opinion that the leprosy bacillus can be detected in the nasal mucus, the majority believe that the earliest lesion is found in the nasal mucous membrane; others are either conservative on this last point or are positive in declaring that the nose is not the site of the primary lesion. A few assert that the bacillus is rarely or never found in the nasal secretions, especially in anesthesic cases.

Morrow states that the bacilli are absent from all physiologic secretions. McDonald, with regard to the bacillus in physiologic secretions, makes this statement: "After many faithful trials in every stage of the disease, I have found them so seldom that I now attach but little importance to it as a means of diagnosis." Black and Schilling state that the bacilli are not found in the nasal secretions of anesthesic or macular cases. Turner writes, "Never yet have I seen an ulcer in the nasal passages appear as a first indication of leprosy; it is rarely an early lesion."

The following paragraph from Mercier's article on Leper Houses and Mediaeval Hospitals, wherein he quotes from John Trevisa's translation from the Latin of Bartholemy Glanville, may be of interest. "Redde Whelkes and

Pymples in the face — out of whom oftenne runne Blood and Matter; in such the nose swellen and ben grete, the vertue of smellynge fayleth and the Brethe stynkyth right fowle."

Sputum.—As is well known, the mouth, pharynx, larynx, and vocal cords are commonly affected in leprosy; the bronchi and lungs relatively seldom. Therefore, the fact that bacilli are found may indicate either that the bacilli are most likely from the open lesions located in different parts of the respiratory tract, or that tuberculosis of the lungs is superimposed on leprosy. Unless investigators can exclude by animal inoculation the possibility that tuberculosis is present, the results obtained by examining sputum are of little importance.

The following are the only references on this phase of the subject that I have been able to find.

Besnier notes that the sputum usually contains numerous bacilli. Bibb found the bacillus occasionally in the sputum. Sticker reported that the sputum of 83 percent of his cases was positive. Spiegel found it swarming with bacilli in cigar-like masses. Uhlenhuth and Steffenhagen, by using antiformin, demonstrated the presence of the bacilli in sputum. Hollmann found it positive in only one case out of a total of thirty-one. Rosenau states that the bacillus does not occur in the expectoration from the lungs.

Saliva.—To a large extent the same is true of examination of the saliva. Consequently, unless the methods used by investigators are given, the results are of little value. Leloir states that he found the bacillus of leprosy in the saliva, but modifies his statement by saying that the surfaces must be infected. Morrow affirms that the bacillus is not found in the saliva, but Hollmann found the saliva to contain the bacillus in 21.7 percent of his cases of leprosy, all of the nodular type.

Urine.—The failure of investigators to state their methods in obtaining the urine and the fact that the exterior of the genitals is liable to be soiled and is often found to be the site of open lesions, makes the value of their results questionable. Interest is increased by the fact, quoted by Arning, that the Chinese believed the urine responsible for the spread of the disease. Many authors state that the bacillus is found in the urine but only during febrile exacerbations of the disease, and others that the bacillus can be induced by drugs to appear in the urine.

Arning, in his report to the Board of Health of Hawaii in 1886, Besnier and also Leloir, Morrow, McNutt, Bibb and McLeod — all state that the bacillus cannot be found in the urine. Since their work was done, however, there have been many statements to the contrary. The positive results may be entirely due to an improvement in technic. Lagane in 1912 and 1913 reports finding the bacillus in four of five cases. He states, however, that the bacilluria is irregular, the bacilli probably appearing only during an acute attack. In three of his cases, the bacilli appeared after the giving of arsenobenzol. Rosenau believes that they are only occasionally found. DeBeurmann and Gougerot found the bacilli in the urine. Hollmann found it in 7.1 percent of his cases, eight being nodular leprosy. Stitt states that the "bacilli may be eliminted by the urine during occasions of fever."

Blood.—The presence of the bacillus in the blood is a more important question and has some bearing on the problem of transmission of the disease through the bite of insects. The technic is also important.

Ziemssen (1885) states that he had never succeeded in a single instance in demonstrating bacilli in the lumen of blood vessels, or with dry preparations of blood. He notes, however, that if blood is drawn from leprous lesions, bacilli get into the escaping blood mechanically. Arning also states that if the blood is taken with all due precaution it does not contain the bacillus. Leloir after many preparations from five cases found the bacillus in one case. He thinks that the blood does not contain the bacillus permanently and that if it is introduced into the blood, it disappears rapidly. Besnier states that the bacillus is absent.

Hyde states that "their occurrence in the blood, an essential point in the demonstration of their etiologic importance, has been recognized solely by Hillairet and Gaucher." Neisser also declares that he never found the bacilli in the circulating blood. Müller, Köbner (quoted by Wolters), and also Majocchi and Pellizari (quoted by Ziemann) found the bacilli in the blood during the eruptive period. Jaja always found the bacilli in the blood, but his methods of skin puncture probably account for this result. Cornil and Babes found the bacilli in the blood by puncturing glands. (Here evidently the bacilli were from the gland tissue and not from the circulating blood.) Morrow states that the bacillus is not found in the blood. McNutt asserts that it cannot be found in the blood, not even during the febrile attacks. Bibb and Klingmuller found the bacilli in the blood. Gravagna-Catania's statement is of importance. In two of his cases, which were supposed to be stationary cases, the bacilli were found in the blood. Deycke-Pascha, performing an autopsy on a case of leprosy in a Jew, found that the blood contained many leprosy bacilli. Marchoux found them in the blood and not during the fever period. He also quotes Wolters, Wolff, and Doutrelepont as having found them in the blood. Ohashi found the blood positive in 80 percent of nodular, and 20 percent of anesthesic cases. Sugai and Monobe report six of ten cases positive; they also found the bacilli in the placenta of two of five anesthesic cases, in two of seven nodular cases, in the blood of ten of twelve new-born children, and also in a seventeen-month-old child. Crow reports the finding of the bacilli in twenty-one of twenty-four cases, of different types of the disease, mostly nodular. Manson states that they occasionally occur free in the blood or in leukocytes; he also states that if tuberculin is given it causes the appearance of bacilli in the blood. Lagane, in examining three cases of different types, did not, on first examination, find the bacillus, but, upon giving arsenobenzol, found it in both urine and blood in two cases. Kalindero found it in one case. In 1913 we have a long series of favorable reports on the presence of the bacilli in the blood. DeBeurmann and Gougerot, Rabinowitsch and Reenstierna give positive, altho limited, reports. Thibault examined the blood of thirty patients and found the bacilli in seven. Stitt sums up the results by stating that the "leprosy bacilli are apt to be found in the blood of nodular cases, especially at the time of the febrile accessions," and that the "bacilli are present in the blood of cases of nodular leprosy rather constantly but less so in that of cases of nerve leprosy." Turner states that "the bacillus of leprosy may be met with wherever the blood circulates. To see them clinging to the endothelium of the capillaries causes one to wonder that they are not more common in the circulation."

Numerous statements appear regarding the finding of the lumen of blood vessels filled with bacilli, the presence of thrombi and occlusion of the vessels. Gluck, Danielssen, and Boeck all give details of the changes found in the blood vessels, the infiltration and thickening of the adventitia, small cell infiltration of the muscularis, and a high grade thickening of the intima, with numerous masses of bacilli scattered throughout, the infiltration of the same, and new formation of vessels. These changes all point to the reason for the presence of bacilli in the blood stream.

Feces.—The consensus of opinion is that ulceration of the intestine is necessary to the bacillus' being found in the intestinal discharges. It is also likely that material from the mouth, nose, and throat containing large numbers of bacilli may be swallowed. It is probable also that the bacilli may be found apart from these two causes.

Arning thought that the feces might play a part in spreading the disease, especially in primitive communities. The bacilli will be found especially in diarrhea. In 1886, in his report to the Hawaiian Board of Health, he again mentions finding the bacilli in the feces. Bibb never found the bacilli in the feces. Boeck also lays stress on the danger of the feces spreading the disease, having found the feces positive in one of three cases. Galli-Valerio, by treating the feces with antiformin, found the bacilli in both of two cases. Manson is doubtful whether they occur in the intestinal tract. Merian found the bacilli in two of three nodular cases, potassium iodid having been given in one case. Hollmann reports negative results in four cases.

It is rather surprising to find that so few report on this point. One difficulty, however, is recognized in the making of preparations from feces. The presence of an enormous number of organisms—some of them similar to the leprosy bacilli—necessitates the most careful search to obtain any result. It is wise therefore to be conservative in making any report of a positive nature.

Other secretions.—Regarding the presence of bacilli in other secretions, very few references are found. Leloir found the bacilli in the sperm, but not in the uterine or vaginal secretions. Klingmüller found it also in the sperm. Sugai and Monobe found it in the milk of two of twelve cases. English found it in the conjunctiva, and Hollmann found the bacilli in the sweat and tears in

14.2 percent of nodular cases. Besnier also reports finding them in the tears. Leloir states again that if the surfaces are infected the bacilli will be found in the tears.

METHODS

Feces.—Sterile porcelain jars were used for the collection of the specimens, from which a small amount, approximately one-fourth square inch, was taken and placed in 25 c.c. of 10 percent antiformin, thoroughly stirred, and allowed to stand for one hour; this was well shaken three or four times during the hour. One-half of the mixture was then transferred to a centrifuge tube and centrifugated for fifteen minutes, decanted, and the sediment washed in sterile water; once again it was centrifugated, decanted, and washed. After one more decanting, part of the sediment was spread fairly thick on a slide, fixed, and stained.

Sputum.—The usual method of collecting and making smears as for tuberculosis was used. Later it was found that using antiformin, washing with sterile water, and examining the sediment after centrifugation was the better method.

Nasal smears.—These were obtained directly from the free excretion (when obtainable). Smears were made, by means of a small, tightly woven cotton swab, directly on to clean slides. Tears were obtained in the same manner.

Urine.—In all cases during the last examination care was taken to have the external genitals clean, to discard the first part of the urine, and to see that the receptacles were sterile. Care was also taken that the hands of the patients should not come into contact with the urine or the receptacle. More care was exercised here than with any of the other specimens. The urine was examined on the same day as when passed and before examination was well shaken. All urine was centrifugated for thirty minutes. In a few cases, the sediment was treated with antiformin, washed with sterile water, and then the sediment examined; this method was used when the sediment was injected into guinea-pigs. Smears were made from the sediment after decanting the fluid. It was learned that if the bacilli were easily found in any given specimen it mattered very little how the sediment was obtained and treated. In all questionable cases, the urine sediment or the sputum was injected into guinea-pigs.

Blood.—This was obtained from the median vein at the bend of the arm because the skin here is seldom affected by the disease. By means of a sterile syringe, 5-10 c.c. of blood were taken and immediately emptied into a centrifuge tube containing a given hemolytic solution. Three methods of treating the blood were used, often two methods in the same case:

(*a*) By Crow's method take 5 c.c. of venous blood and put into a tube with 5 c.c. of a 2 percent sodium citrate in normal salt solution. Invert tube a few times, plug, place in cold place for sediment and next day take upper layer of sediment. Make thick smears, dry, place in distilled water five to fifteen minutes, then dry, fix and stain.

(*b*) By the Kurashigi-Schnitter method, take 1 c.c. of venous blood and put into a tube with 5 c.c. of a 3 percent acetic acid solution. Allow to stand one-half hour, centrifugate one-half hour, decant. Dissolve sediment in 5 c.c. of concentrated antiformin and when dissolved add 5 c.c. absolute alcohol, centrifugate one-half hour, decant, and wash sediment in distilled water, centrifugate again, and spread sediment on slides and stain.

(*c*) By Rabinowitsch's method, take 10 c.c. of venous blood and put into a tube with 10 c.c. distilled water with 1 percent sodium citrate (sapotoxin can also be added). Shake, centrifugate, and decant. Wash sediment in distilled water, decant, and then add 10 percent antiformin solution and let stand one hour at 37 C. Centrifugate, decant, and wash sediment in distilled water, decant, and spread sediment on slides and stain.

In some instances, modifications were made in these methods, but the Kurashigi-Schnitter method proved by far the most satisfactory. In the preparation of all specimens, two smears were made in each case and in some instances, more. All smears were fixed by heat and all staining was done with carbolfuchsin (Verhoeff's solution) as follows: the smear was steamed for thirty seconds, decolorized with 1 percent acid-alcohol for various lengths of time, according to the thickness of the smear, washed thoroughly, and counterstained with Loeffler's methylene blue. In some instances, 95 percent alcohol was used as a decolorizing agent in case acid-alcohol was not sufficient in thick smears.

GENERAL RESULTS

Blood.—Of 28 examinations among 16 patients, there were 9 positive, 3 questionable, and 16 negative. This represents 8 patients with positive and 8 patients with negative results.

Urine.—Of 41 examinations made on 16 patients, 16 were positive in 9 patients.

Feces.—Of 27 examinations of 16 patients, 10 were positive in 6 patients.

Sputum.—Here the positive results were more frequent: Of 41 results recorded among 16 patients, 32 were positive and 9 negative, 14 patients giving positive and 2 patients negative sputum.

Nasal Mucus.—Sixteen patients with 41 examinations gave 34 positive, 6 negative, and 1 questionable result. In other words, 14 patients had bacilli in the nasal mucus and 2 did not.

Ulcerations.—Of 15 patients that had bullae, ulcers, and pustules, those having bullae gave 5 results positive and 10 negative; ulcers, 13 positive and 2 negative; and pustules, 7 positive and 8 negative.

Tears.—Negative in 26 examinations with 13 patients.

GENERAL DISCUSSION

In view of the criticism of previous papers in this respect, care was taken to obtain, prepare, and stain specimens as uniformly as possible. Every precaution was taken to eliminate outside bacteria; that is, by the use of sterile water, clean slides, etc. Examining the slides was an extremely arduous task, consuming an enormous amount of time and patience. No slide was considered positive unless bacilli were found in several fields or, in the case of sputum or similar specimens, in groups. In examining the specimens, a large number of organisms were found, some acid-fast and some similar in many respects to the acid-fast bacillus of leprosy. The blood was not taken during febrile attacks. No acid-fast bacilli other than those agreeing with the type of Hansen were considered, and to avoid error of judgment, reference was frequently made to slides obtained from lesions of leprosy showing typical bacilli, singly and in groups. Apart from the three series of examinations, a great number of individual examinations have been made during the two years and notes kept of the results. Smears were made on the same day that specimens were obtained; in the case of urine, this precaution was obviously necessary. In the case of blood, urine, and fecal specimens, the possibility of the presence of local lesions was kept in mind. Lesions in the kidneys are extremely rare; intestinal ulceration is more common.

From the table representing examinations in June and December, 1914, and March, 1915, it will be seen that the results are uniform from the three series in only a few cases. In one case, an anesthesic, there was only one positive result. It may have been an error in technic that there were not more positive results. The nasal secretions and sputum gave the greatest number of positive and uniform results. The fact that the air passages are so early and seriously affected and constantly irritated and that bacilli from open lesions can so easily be taken up by the secretions, will account for the great number of positive findings. The four cases which gave the largest number of positive results were all ulcerative nodular cases, in a very advanced stage of the disease. The feces and the blood gave the least number of positive results. It is difficult to understand why the specimens of feces did not show better results, as, I believed, the sputum swallowed might also have added to the frequency of the occurrence of the bacilli. During diarrhea, the bacilli were more easily and more abundantly found. They were found however in cases which did not suffer from intestinal disturbances. The blood and urine should have given more uniform results, and, in cases where the bacilli were fairly readily found in the urine, a more eager attempt was made to find the bacilli in the blood specimens. The findings in the smears from ulcers, bullae, etc., need no further explanation.

TABLE 1

Results of the Examination of Blood, Etc., to Determine the Presence of Acid-Fast Bacilli

Patient	Type of Disease	Stage	Blood		Urine			Sputum			Feces		Nasal Mucus			Tears	Bullae	Ulcers	Pustules
			June 1914	March 1915	June 1914	Dec. 1914	March 1915	June 1914	Dec. 1914	March 1915	Dec. 1914	March 1915	June 1914	Dec. 1914	March 1915	March 1915	June 1914	June 1914	June 1914
F. B.	Nodule ulcerative	Advanced.....	0	+	+	+	+	+	+	+	0	+	+	+	+	0	0	+	+
*†I. B.	Mixed.......	Advanced.....	0	0	0	0	+	+	+	+	0	0	+	+	+	0	+	+	0
†M. C.	Nodular.....	Far advanced	+	+	0	0	0	+	+	+	0	+	+	+	+	0	0	+	0
M. G.	Nodular.....	Advanced.....	0	+	0	0	+	+	+	+	+	+	+	+	+	0	+	+	0
*L. D.	Mixed.......	Advanced.....	0	+	0	0	0	+	0	0	0	0	+	?	0	0	0	+	+
*S. G.	Nodular.....	Advanced.....	0	0	+	+	+	+	+	+	+	+	+	+	+	0	0	+	+
M. M.	Anesthesic..	Far advanced	0	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0
†L. P.	Nodular.....	Advanced.....	0	+	0	0	0	0	+	+	0	0	+	+	+	0	+	+	0
W. Q.	Nodular.....	Early.........	+	?	0	0	0	0	+	+	0	0	+	0	+	0	0	+	+
*A. T.	Mixed.......	Advanced.....	?	+	+	+	0	+	+	+	+	+	+	+	+	0	+	+	0
Y. T.	Nodular ulcerative	Advanced.....	0	?	+	0	+	+	+	+	+	+	+	+	+	0	+	+	0
†I. U.	Nodular ulcerative	Advanced.....	0	N.Ex.	0	0	+	+	+	+	0	0	+	+	+	0	0	+	+
H. K.	Nodular.....	Early.........	..	+	0	0	+	0	0	+	0	0	+	+	+				
H. O.	Anesthesic..	Early.........	0	..	0	..	..	0	..	..	..	..	0	..	..	..	0	0	0
*F. P.	Nodular.....	Far advanced	0	..	0	..	..	+	..	..	..	..	+	..	..	..	0	+	+
J. N.	Nodular.....	Far advanced	0	..	0	..	..	+	..	..	..	..	+	..	..	..	0	+	+

* Epistaxis occurred in these cases.

† Diarrhea occurred in these cases.

Blood was not examined during febrile attacks.

It is evident, therefore, that the only question which materially interferes with the conclusions is the inability to identify absolutely the acid-fast bacillus as being the acid-fast bacillus of leprosy. The possibility of its being the tubercle bacillus can be ruled out by the failure to obtain positive results by animal inoculation or by cultivation. Inoculations of guinea-pigs with the sediment of urine and sputum resulted negatively. The numerous cultivation experiments for an acid-fast bacillus have also proved negative. To a certain extent, the possibility of an acid-fast bacillus from water or contamination is unlikely, on account of the care taken to avoid this possibility. The routine method of treating, staining, and examining specimens, the adherence to a type bacillus, and especially the fact that the bacilli occurred in groups lessens the chance of error that we are dealing with other than the acid-fast bacillus of leprosy. In many respects, the questions raised here are similar to those which have been discussed in tuberculosis.

CONCLUSIONS

Bacilli resembling the typical acid-fast bacilli of leprosy were found in the circulating blood and excretions examined, frequently enough to warrant the statement that the blood, urine, feces, sputum, nasal excretions, etc., contain the bacilli and consequently may play a part in the spread of the disease, especially where unhygienic conditions prevail and the disease is prevalent.

The occurrence of symptoms of toxic-febrile attacks, etc., are more easily understandable when the fact is accepted that the bacilli are found in the blood stream and excretions.

The presence of bacilli in the blood and in the various excreta as determined, warrants the assumption that insect transmission of leprosy is a possibility.

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